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Lung damage assessed by CT scan was not predictive in 6 year-old CF children: a case control study of a neonatal screened population

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Recent reports enhanced the use of scored CT scan in early lung damage in CF. A case control study was performed to assess the outcome at age 6y of a screened (S) compared to an unscreened (US) population, treated in two centres with similar procedures.

Respiratory and digestive history of 33 S (Rouen) and 49 US infants (Toulouse) was collected, including PFTs and scored chest CT scan. A Bhalla modified score comprised of bronchial wall thickening (BWT), bronchiectasis, atelectasis, mucus plugs and air-trapping (AT) evaluation was used (Robinson TE, J Pediatr. 2001). A normal score was 42.

CT scan showed early mild lung damage in 81.8% patients in S and 81.6% in US. Total and detailed scores were similar in both groups. BWT was significantly more frequent than atelectasis, mucus plugging and AT ($p<0.001$), and right upper lobe (RUL) significantly more affected than lingula ($p<0.001$). CT scan score was correlated with FEF25/75 in both groups. Extent and severity of bronchiectasis in all children were inversely correlated with BMI, FEV1, and FEF25/75. No relationship was found between the onset or type of microbiological colonization, and the CT scan score or PFTs studied.

Early diagnosis of CF did not appear to influence the lung damage observed at age 6, and no predictive factor was identified. Bronchiectasis was related to altered PFTs, nutritional status and signed a worsening disease. Early lung damage, correlated to the small airway disease and BWT being the most widespread damage independently of colonization, might be the results of an early non-specific inflammation in CF lung disease.

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The effect of genotype on sweat test values

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Background: The challenge for clinicians is to be able to exclude a diagnosis of CF and to identify atypical cases in whom the diagnosis may have been missed.

Aims: To compare sweat test values in patients with CF according to the number of identified mutations and to describe the relationship between mutation class and sweat sodium and chloride values.

Methods: 192 patients attended the Regional CF units between 1 July 1994 and 30 June 2004 for an assessment that included mutation analysis. 169 of these patients also had a sweat test performed. A total of 34 different mutations were identified with DF508 being the most common (gene frequency 63.5%). The mutation was unknown in 9.3% of chromosomes. 17 patients (8.9%) had normal or borderline sweat tests. The mild mutations R117H, D1152, 3849+10kb(C>T) accounted for 41% of CF genes in this group.

Results: Median (range) sweat sodium and chloride concentrations were 91 (15-141) and 98 (19-160) respectively for 2 identifiable mutations, 78.5 (49-116) and 86 (37-113) for 1 mutation and 103 (93-125) and 103 (95-140) in the absence of any mutations. Sweat chloride results were borderline for 8 patients with two mutations and normal in three patients with two mutations and one patient with a single mutation. All patients with no CF mutations had unequivocal sweat test results.

Normal sweat test results were associated with R117H 7T (n=3) and D1152 + other.

Conclusion: In a small minority of patients the diagnosis of CF remains a clinical diagnosis and further electrophysiological tests are necessary.

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R117H-7T: clinical outcome of the newborns screened in Brittany with this variant

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The clinical evolution of subjects compound heterozygous for a severe *CFTR* mutation and the R117H-7T remains unclear and it is difficult to provide a fully satisfactory genetic counselling to the concerned families. In France, this constitutes a real matter as the R117H is detected by the kit used in the nationwide newborn screening (NS) program and appears the most frequent anomaly after the F508del (7.4%). The aim of this study was to describe the clinical outcome of the R117H compound heterozygotes screened in Brittany (western France) where a pilot experience of NS was set up in 1989 and where CF is frequent. Data on clinical status was obtained near the French CF Registry or directly near paediatricians. From 1989 to 2004, 565 546 newborns were screened for CF in Brittany, among whom 195 had an elevated IRT and two *CFTR* mutations. Nine of these children (4.6%) were compound heterozygotes for the R117H, which was in all cases linked to the 7T variant (F508del/R117H (n=7), I507del/R117H or G551D/R117H). Current mean age of these children is 5.7 y. [2.6-9.5]. Sweat chloride level, which was lower than 30 mEq/L in four children, was in mean 37.7 mEq/L (σ=14.3). All the children are pancreatic sufficient. Their nutritional status and growth appear normal (height-zcore: 0.5 (σ=1.0); weight-zscore: -0.1 (σ=1.5)) and spirometric data, available for two children, are perfect (FVC: 117.5%; FEV1: 109.4%). None of the children carrying a R117H-7T has yet developed signs of CF. As it has been reported that this allele could be associated with some pulmonary symptoms, it is important to maintain their follow-up in order to check the appearance of any clinical signs.

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Screening of defective cystic fibrosis (CF) genomes: Two different approaches, one to be favored

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According to some thought trends, heterozygote carrier systematic screening (HCSS) could noticeably decrease, or even eradicate cystic fibrosis (CF) in populations. In a recent past, there were two possible approaches, one adopted with macro-populations (on the scale of a country or province, etc.), called "mass screening programs", the other with micro-populations (nuclear or extended family, at-risk communities, etc.), called "cascade heterozygote screening".

A multidisciplinary analysis (clinician, geneticist, ethicist) submitted this double approach to the test of historical experience and bioethics principles (beneficience/non-maleficience, autonomy, justice and equity).

(1) From a theoretical point of view, carrier screening in macro-populations may appear commendable, but is in reality utopian for disease eradication: a) on the financial level, the cost/benefit ratio (diverse resources and infrastructures vs. population health) would be too high; (b) on the social and moral level, laws should be passed and pressure put on people so that they accept to submit to HCSS. (2) Selective screening in micro-populations is a more realistic approach: (a) small number of individuals or families included in a clinician/patient relationship; (b) greater respect of values, autonomy and equity; (c) better control of genetic information (job, insurance, etc.); (e) reduction of financial costs; (f) better access to health care, help and follow-up in genetic counselling.

The conducted analysis shows that cascade heterozygote screening for CF is a method to be favored in view of screening experience and ethical and social values in a democratic society.

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